CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074736
Trade Name : PENTAZOCINE AND NALOXONE TABLETS

Generic Name: Pentazocine and Naloxone Hydrochloride Tablets

Sponsor : Royce Laboratories, Inc.

Approval Date: January 17, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074736

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter			X	
Approvable Letter				X
Final Printed Labeling	X			
Medical Review(s)				X
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)	X			
Administrative Document(s)				X
Correspondence				X

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074736

APPROVAL LETTER

ANDA 74-736

Royce Laboratories, Inc.
Attention: Loren Gelber, Ph.D.
16600 N.W. 54 Avenue
Miami, FL 33014

Dear Madam:

This refers to your abbreviated new drug application dated August 30, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Pentazocine and Naloxone Hydrochlorides Tablets, USP, 50 mg (base)/0.5 mg (base).

Reference is also made to your amendments dated December 7, 1995, April 9, and July 31, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Pentazocine and Naloxone Hydrochlorides Tablets, USP, 50 mg (base)/0.5 mg (base), are bioequivalent and, therefore therapeutically equivalent to the listed drug (Talwin NX Tablets, 50 mg (base)/0.5 mg (base), of Sanofi Winthrop Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

[redacted] 1/17/97

Deputy Center Director for Pharmaceutical Science
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-736
ANDA #74-736/Division File
Field Copy
HFD-600/Reading File
HFD-92
HFD-610/J.Phillips
HFD-8/P.Savino

Endorsements:

HFD-627/L.Huang/1-[redacted]
HFD-613/C.Holquist[redacted]
HFD-613/J.Grace/[redacted]
HFD-627/P.Schwartz[redacted]
HFD-617/J.Buccine,[redacted]
Drafted J.Buccine/[redacted]
X:\NEW\FIRMSNZ\ROYCE\LTRS&REV\74736.AP
F/T by MM January 2, 1997

APPROVAL - FIRST GENERIC

[redacted]

[redacted]

First generic approval
Cadid for cGMP section
is satisfactory
1/8/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074736

FINAL PRINTED LABELING

NDC 51875-0395-1

Royce™

Pentazocine and Naloxone Hydrochlorides Tablets, USP

C IV

50 mg*/0.5 mg*

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

*Each tablet contains: Pentazocine Hydrochloride, USP equivalent to 50 mg of pentazocine and Naloxone Hydrochloride, USP equivalent to 0.5 mg of naloxone.

Usual Adult Dosage: One tablet every three or four hours; may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets. See accompanying insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.

Batch No.:

Exp. Date:

N 3 51875-0395-1 1

NDC 51875-0395-1

Royce™

Pentazocine and Naloxone Hydrochlorides Tablets, USP

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Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.

Batch No.:

Exp. Date:

N 3 51875-0395-1 1

NDC 51875-0395-2

Royce™

Pentazocine and Naloxone Hydrochlorides Tablets, USP

C IV

50 mg*/0.5 mg*

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

*Each tablet contains: Pentazocine Hydrochloride, USP equivalent to 50 mg of pentazocine and Naloxone Hydrochloride, USP equivalent to 0.5 mg of naloxone.

Usual Adult Dosage:
One tablet every three or four hours; may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets. See accompanying insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.

Batch No.:

Exp. Date:

N 3 51875-0395-2 8

NDC 51875-0395-2

Royce™

Pentazocine and Naloxone Hydrochlorides Tablets, USP

C IV

50 mg*/0.5 mg*

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

*Each tablet contains: Pentazocine Hydrochloride, USP equivalent to 50 mg of pentazocine and Naloxone Hydrochloride, USP equivalent to 0.5 mg of naloxone.

Usual Adult Dosage:
One tablet every three or four hours; may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets. See accompanying insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.

Batch No.:

Exp. Date:

N 3 51875-0395-2 8

NDC 51875-0395-2

Royce™

Pentazocine and Naloxone Hydrochlorides Tablets, USP

C IV

50 mg*/0.5 mg*

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

*Each tablet contains: Pentazocine Hydrochloride, USP equivalent to 50 mg of pentazocine and Naloxone Hydrochloride, USP equivalent to 0.5 mg of naloxone.

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One tablet every three or four hours; may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets. See accompanying insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.

Batch No.:

Exp. Date:

N 3 51875-0395-2 8

NDC 51875-0395-4

Royce™

Pentazocine and Naloxone Hydrochlorides Tablets, USP

C IV

50 mg*/0.5 mg*

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

*Each tablet contains: Pentazocine Hydrochloride, USP equivalent to 50 mg of pentazocine and Naloxone Hydrochloride, USP equivalent to 0.5 mg of naloxone.

Usual Adult Dosage:
One tablet every three or four hours; may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets. See accompanying insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.

Batch No.:

Exp. Date:

N 3 51875-0395-4 2

NDC 51875-0395-4

Royce™

Pentazocine and Naloxone Hydrochlorides Tablets, USP

C IV

50 mg*/0.5 mg*

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

*Each tablet contains: Pentazocine Hydrochloride, USP equivalent to 50 mg of pentazocine and Naloxone Hydrochloride, USP equivalent to 0.5 mg of naloxone.

Usual Adult Dosage:
One tablet every three or four hours; may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets. See accompanying insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.

Batch No.:

Exp. Date:

N 3 51875-0395-4 2

NDC 51875-0395-4

Royce™

Pentazocine and Naloxone Hydrochlorides Tablets, USP

C IV

50 mg*/0.5 mg*

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

*Each tablet contains: Pentazocine Hydrochloride, USP equivalent to 50 mg of pentazocine and Naloxone Hydrochloride, USP equivalent to 0.5 mg of naloxone.

Usual Adult Dosage:
One tablet every three or four hours; may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets. See accompanying insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.

Batch No.:

Exp. Date:

N 3 51875-0395-4 2

PENTAZOCINE AND NALOXONE HYDROCHLORIDES TABLETS, USP

C IV

Analgesic for Oral use Only

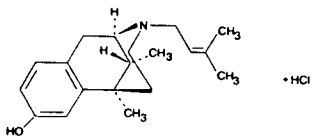
Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe, potentially lethal, reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in a combination with other substances. (see DRUG ABUSE AND DEPENDENCE section.)

DESCRIPTION

Pentazocine and naloxone hydrochlorides tablets, USP contain pentazocine hydrochloride, USP, equivalent to 50 mg base, a member of the benzazocine series (also known as the benzomorphan series), and naloxone hydrochloride, USP, equivalent to 0.5 mg base.

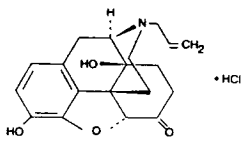
Pentazocine and naloxone hydrochlorides tablet is an analgesic for oral administration.

Chemically, pentazocine hydrochloride is a (2*R**, 6*R**, 11*R**)-1,2,3,4,5,6-Hexahydro-6, 11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride, a white, crystalline substance soluble in acidic aqueous solutions. It has the following structural formula:



$C_{19}H_{27}NO \cdot HCl$ Molecular Weight 321.89

Chemically, naloxone hydrochloride is 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. It is a slightly off-white powder, and is soluble in water and dilute acids. It has the following structural formula:



$C_{19}H_{21}NO_4 \cdot HCl$ Molecular Weight 363.84

Each tablet, for oral administration, contains pentazocine hydrochloride, USP, equivalent to 50 mg of pentazocine, and naloxone hydrochloride, USP, equivalent to 0.5 mg of naloxone. In addition each tablet contains the following inactive Ingredients: colloidal silicon dioxide, D&C yellow #10 Al-lake, FD&C blue #1 Al-lake, FD&C yellow #6 Al-lake, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY

Pentazocine is a potent analgesic which when administered orally in a 50-mg dose appears equivalent in analgesic effect to 60 mg (1 grain) of codeine. Onset of significant analgesia usually occurs between 15 and 30 minutes after oral administration, and duration of action is usually three hours or longer. Onset and duration of action and the degree of pain relief are related both to dose and the severity of pretreatment pain. Pentazocine weakly antagonizes the analgesic effects of morphine and meperidine; in addition, it produces incomplete reversal of cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. Pentazocine has about 1/50 the antagonistic activity of nalorphine. It also has sedative activity.

Pentazocine is well absorbed from the gastrointestinal tract. Concentrations in plasma coincide closely with the onset, duration, and intensity of analgesia; peak values occur 1 to 3 hours after oral administration. The half-life in plasma is 2 to 3 hours.

Pentazocine is metabolized in the liver and excreted primarily in the urine. Pentazocine passes into the fetal circulation.

Naloxone when administered orally at 0.5 mg has no pharmacologic activity. Naloxone hydrochloride administered parenterally at the same dose is an effective antagonist to pentazocine and a pure antagonist to narcotic analgesics.

Pentazocine and naloxone hydrochlorides tablets are a potent analgesic when administered orally. However the presence of naloxone in pentazocine and naloxone hydrochlorides will prevent the effect of pentazocine if the product is misused by injection.

Studies in animals indicate that the presence of naloxone does not affect pentazocine analgesia when the combination is given orally. If the combination is given by injection the action of pentazocine is neutralized.

INDICATIONS AND USAGE

Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe potentially lethal, reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (see DRUG ABUSE AND DEPENDENCE section.)

Pentazocine and naloxone hydrochlorides tablets are indicated for the relief of moderate to severe pain.

Pentazocine and naloxone hydrochlorides tablets are indicated for oral use only.

CONTRAINDICATIONS

Pentazocine and naloxone hydrochlorides should not be administered to patients who are hypersensitive to either Pentazocine or naloxone.

WARNINGS

Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe, potentially lethal reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (See DRUG ABUSE AND DEPENDENCE section.)

Drug Dependence. Pentazocine can cause a physical and psychological dependence. (see **DRUG ABUSE AND DEPENDENCE.**)

Head Injury and Increased Intracranial Pressure. As in the case of other potent analgesics, the potential of pentazocine for elevating cerebrospinal fluid pressure may be attributed to CO_2 retention due to the respiratory depressant effects of the drug. These effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, pentazocine can produce effects which may obscure the clinical course of patients with head injuries. In such patients, pentazocine must be used with extreme caution and only if its use is deemed essential.

Usage with Alcohol. Due to the potential for increased CNS depressant effects, alcohol should be used with caution in patients who are currently receiving pentazocine.

Patients Receiving Narcotics. Pentazocine is a mild narcotic antagonist. Some patients ...

to 3 hours.

Pentazocine is metabolized in the liver and excreted primarily in the urine. Pentazocine passes into the fetal circulation.

Naloxone when administered orally at 0.5 mg has no pharmacologic activity. Naloxone hydrochloride administered parenterally at the same dose is an effective antagonist to pentazocine and a pure antagonist to narcotic analgesics.

Pentazocine and naloxone hydrochlorides tablets are a potent analgesic when administered orally. However the presence of naloxone in pentazocine and naloxone hydrochlorides will prevent the effect of pentazocine if the product is misused by injection.

Studies in animals indicate that the presence of naloxone does not affect pentazocine analgesia when the combination is given orally. If the combination is given by injection the action of pentazocine is neutralized.

INDICATIONS AND USAGE

Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe potentially lethal, reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (see DRUG ABUSE AND DEPENDENCE section.)

Pentazocine and naloxone hydrochlorides tablets are indicated for the relief of moderate to severe pain.

Pentazocine and naloxone hydrochlorides tablets are indicated for oral use only.

CONTRAINDICATIONS

Pentazocine and naloxone hydrochlorides should not be administered to patients who are hypersensitive to either Pentazocine or naloxone.

WARNINGS

Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe, potentially lethal reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (See DRUG ABUSE AND DEPENDENCE section.)

Drug Dependence. Pentazocine can cause a physical and psychological dependence. (see **DRUG ABUSE AND DEPENDENCE.**)

Head Injury and Increased Intracranial Pressure. As in the case of other potent analgesics, the potential of pentazocine for elevating cerebrospinal fluid pressure may be attributed to CO_2 retention due to the respiratory depressant effects of the drug. These effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, pentazocine can produce effects which may obscure the clinical course of patients with head injuries. In such patients, pentazocine must be used with extreme caution and only if its use is deemed essential.

Usage with Alcohol. Due to the potential for increased CNS depressant effects, alcohol should be used with caution in patients who are currently receiving pentazocine.

Patients Receiving Narcotics. Pentazocine is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving pentazocine.

Certain Respiratory Conditions. Although respiratory depression has rarely been reported after oral administration of pentazocine, the drug should be administered with caution to patients with respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma, and other obstructive respiratory conditions, or cyanosis.

Acute CNS Manifestations. Patients receiving therapeutic doses of pentazocine have experienced hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted, it should be done with caution since these acute CNS manifestations may recur.

PRECAUTIONS

CNS Effect. Caution should be used when pentazocine is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of pentazocine though no cause and effect relationship has been established.

Impaired Renal or Hepatic Function. Decreased metabolism of pentazocine by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that pentazocine causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.

In prescribing pentazocine for long-term use, the physician should take precautions to avoid increases in doses by the patient.

Biliary Surgery. Narcotic drug products are generally considered to elevate biliary tract pressure for varying periods following the administration. Some evidence suggests that pentazocine may differ from other marketed narcotics in this respect (i.e., it causes little or no elevation in biliary tract pressures). The clinical significance of these findings, however, is not yet known.

Information for Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should

be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. Pentazocine may cause physical and psychological dependence when taken alone and may have additive CNS depressant properties when taken in combination with alcohol or other CNS depressants.

Myocardial Infarctions. As with all drugs, pentazocine should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Drug Interactions. Usage with Alcohol: See **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility. No long-term studies in animals to test for carcinogenesis have been performed with the components of pentazocine and naloxone hydrochlorides tablets.

Pregnancy Category C. Animal reproduction studies have not been conducted with pentazocine and naloxone hydrochlorides. It is also not known whether pentazocine and naloxone hydrochlorides can cause fetal harm when administered to pregnant women or can affect reproduction capacity. Pentazocine and naloxone hydrochlorides should be given to pregnant women only if clearly needed. However, animal reproduction studies with pentazocine have not demonstrated teratogenic or embryotoxic effects.

Labor and Delivery. Patients receiving pentazocine during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Pentazocine and naloxone hydrochlorides should be used with caution in women delivering premature infants. The effect of pentazocine and naloxone hydrochlorides on the mother and fetus, the duration of labor and delivery, the possibility that forceps delivery or other intervention or resuscitation of the newborn may be necessary, or the effect of pentazocine and naloxone hydrochlorides on the later growth, development, and functional maturation of the child are unknown at the present time.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pentazocine and naloxone hydrochlorides is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

Cardiovascular: Hypotension, tachycardia, syncope.

Respiratory: Rarely, respiratory depression.

Acute CNS Manifestations: Patients receiving therapeutic doses of pentazocine have experienced hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since these acute CNS manifestations may recur.

Other CNS Effects: Dizziness, lightheadedness, hallucinations, sedation, euphoria, headache, confusion, disorientation; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, depression; and rarely tremor, irritability, excitement, tinnitus.

Autonomic: Sweating; infrequently flushing; and rarely chills.

Gastrointestinal: Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress.

Allergic: Edema of the face; dermatitis, including pruritus; flushed skin, including plethora; infrequently rash, and rarely urticaria.

Ophthalmic: Visual blurring and focussing difficulty.

Hematologic: Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia.

Other: Headache, chills, insomnia, weakness, urinary retention, paresthesia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance. Pentazocine and naloxone hydrochlorides tablet is a Schedule IV controlled substance.

There have been some reports of dependence and of withdrawal symptoms with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision while receiving pentazocine orally. There have been rare reports of possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy.

There have been instances of psychological and physical dependence on parenteral pentazocine in patients with a history of drug abuse and rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral pentazocine has resulted in withdrawal symptoms.

In prescribing pentazocine for chronic use, the physician should take precautions to avoid increases in dose by the patient.

The amount of naloxone present in pentazocine and naloxone hydrochlorides (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine. However, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics.

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals.

Pentazocine and naloxone hydrochlorides tablets contain an opioid antagonist, naloxone (0.5 mg). Naloxone is inactive when administered orally at this dose, and its inclusion in pentazocine and naloxone hydrochlorides tablet is intended to curb a form of misuse of oral pentazocine. Parenterally, naloxone is an active narcotic antagonist. Thus, pentazocine and naloxone hydrochlorides tablets have a lower potential for parenteral misuse than the previous oral pentazocine hydrochloride formulation. However, it is still subject to patient misuse and abuse by the oral route.

OVERDOSAGE

Manifestations. Clinical experience of overdosage with this oral medication has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression due to overdosage or unusual sensitivity to pentazocine, parenteral naloxone is a specific and effective antagonist.

DOSAGE AND ADMINISTRATION

Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe, potentially lethal, reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (See **DRUG ABUSE AND DEPENDENCE** section.)

Adults. The usual initial adult dose is 1 tablet every three or four hours. This may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets.

When anti-inflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with this product.

Children Under 12 Years of Age. Since clinical experience in children under 12 years of age is limited, administration of this product in this age group is not recommended.

Duration of therapy. Patients with chronic pain who receive pentazocine and naloxone hydrochlorides orally for prolonged periods have only rarely been reported to experience withdrawal symptoms when administration was abruptly

Other: Headache, chills, insomnia, weakness, urinary retention, paresthesia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance. Pentazocine and naloxone hydrochlorides tablet is a Schedule IV controlled substance.

There have been some reports of dependence and of withdrawal symptoms with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision while receiving pentazocine orally. There have been rare reports of possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy.

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In prescribing pentazocine for chronic use, the physician should take precautions to avoid increases in dose by the patient.

The amount of naloxone present in pentazocine and naloxone hydrochlorides (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine. However, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics.

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals.

Pentazocine and naloxone hydrochlorides tablets contain an opioid antagonist, naloxone (0.5 mg). Naloxone is inactive when administered orally at this dose, and its inclusion in pentazocine and naloxone hydrochlorides tablet is intended to curb a form of misuse of oral pentazocine. Parenterally, naloxone is an active narcotic antagonist. Thus, pentazocine and naloxone hydrochlorides tablets have a lower potential for parenteral misuse than the previous oral pentazocine hydrochloride formulation. However, it is still subject to patient misuse and abuse by the oral route.

OVERDOSAGE

Manifestations. Clinical experience of overdosage with this oral medication has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression due to overdosage or unusual sensitivity to pentazocine, parenteral naloxone is a specific and effective antagonist.

DOSAGE AND ADMINISTRATION

Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe, potentially lethal, reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (See **DRUG ABUSE AND DEPENDENCE** section.)

Adults. The usual initial adult dose is 1 tablet every three or four hours. This may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets.

When anti-inflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with this product.

Children Under 12 Years of Age. Since clinical experience in children under 12 years of age is limited, administration of this product in this age group is not recommended.

Duration of therapy. Patients with chronic pain who receive pentazocine and naloxone hydrochlorides orally for prolonged periods have only rarely been reported to experience withdrawal symptoms when administration was abruptly discontinued (see **WARNINGS**). Tolerance to the analgesic effect of pentazocine has also been reported only rarely. However, there is no long-term experience with the oral administration of pentazocine and naloxone hydrochlorides.

HOW SUPPLIED

Pentazocine and Naloxone Hydrochlorides Tablets, USP are light green, scored, capsule shaped tablets. They are marked (debossed) 395 to the left of the score and 50 over 0.5 to the right of the score. They have the Royce logo on the reverse side.

SIZE	ROYCE NDC NUMBER
Bottles of 100	51875-0395-1
Bottles of 500	51875-0395-2
Bottles of 1000	51875-0395-4

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by
Royce Laboratories, Inc.
16600 N. W. 54 Avenue, Miami, FL 33014

Revised 03/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074736

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 74-736

3. NAME AND ADDRESS OF APPLICANT

Royce Laboratories, Inc
Attention: Loren Gelber, Ph.D.
16600 N.W. 54 Avenue
Miami, FL 33014

4. LEGAL BASIS OF SUBMISSION:

No Patent or any marketing exclusivity rights are in effect.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pentazocine and Naloxone Hydrochloride USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Applicant:
8/30/95 Original Submission
12/7/95 Biostudy Amendment
4/9/96 Biostudy Amendment
7/31/96 Major Amendment
FDA:
10/6/95 Acknowledgement
3/13/96 Deficiency letter issued

10. PHARMACOLOGICAL CATEGORY

Analgesic (Relief of moderate to severe pain)

11. Rx or OTC RX

12. RELATED IND/NDA/DMF(s)

Listed Drugs: Talwin ® Nx
Holder: Sanofi Winthrop
NDA Number: 18-733
For DMF's details please refer to [redacted](b)4 - Confidential[redacted]

13. DOSAGE FORM

Tablet

14. STRENGTH

50 mg Pentazocine(base)/0.5 mg Naloxone(base)

15. CHEMICAL NAME AND STRUCTURE

Pentazocine: (2R*,6R*,11R*)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride
Mol wt 321.89 Mol formula $C_{19}H_{27}NO.HCl$
For structure please refer to USP 23, page 1184.

Naloxone HCl: 17-Allyl-4,5∝-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate
Mol wt 363.84 Mol formula $C_{19}H_{21}NO_4$
For structure please refer to USP 23, page 1049.

Note: Naloxone HCl exists as anhydrous and a dihydrate

16. COMMENTS

Firm's responses in the areas of deficiencies (Amendment dated 7-31-96) were evaluated to be satisfactory.

17. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

18. RECORDS AND REPORTS
N/A

19. REVIEWER: DATE COMPLETED:
Liang-Lii Huang, Ph.D. December 18, 1996
Endorsed by P.Schwartz, Ph.D. December 19, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074736

BIOEQUIVALENCE REVIEW(S)

J W

ANDA 74-736

OCT 25 1996

Royce Laboratories, Inc.
Attention: Loren Gelber, Ph.D.
16600 NW 54 Avenue
Miami FL 33014

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Pentazocine Hydrochloride and Naloxone Hydrochloride Tablets USP, 50 mg (base) and 0.5 mg (base).

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 8 1996 D N

Pentazocine HCl and Naloxone HCl
50 mg/0.5 mg Tablets
ANDA #**74736**
Reviewer: ZZ Wahba
file #74736a1.496

Royce Laboratories, Inc.
Miami, Florida
Submission date:
April 09, 1996

AMENDMENT TO REVIEWED IN VIVO BIOEQUIVALENCE STUDY UNDER FASTING AND NON-FASTING CONDITIONS

BACKGROUND

The firm has previously submitted two in vivo bioequivalence studies (single-dose fasting and single-dose post-prandial) comparing its test drug product, Royce's Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablets comparing it to the reference drug product, Sanofi Winthrop's Talwin® NX Tablets.

The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated February 12, 1996, ANDA #74-736) due to problems cited in the deficiency comments.

In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

Comment #1a

Provide the raw data of the long-term freezing (-20°C) stability (the stability data should cover the entire length of the study). In addition, the raw data of the effect of room temperature during handling of the samples, and the effect of freeze and thaw cycles should be included.

Response to Comment #1a.

- Long term stability data showed that pentazocine was found to be stable in stock solution and quality control samples for a period of time up to 19 months and 17 months, respectively.
- pentazocine was found to be stable during three freeze/thaw cycles as well as up to 24 hours at room temperature.

The firm's response to comment #1a is acceptable.

Comment #1b

Provide the raw data of pentazocine-recovery analytical methodology.

Response to Comment #1b

Pentazocine recovery data showed that the mean value of pentazocine recovery was 112%.

The firm's response to comment #1b is acceptable.

Comment #1c

Provide statement of the chemical composition (formulation) of the tested drug. The statement should include all active and inactive ingredients and the exact quantity of each component.

Response to Comment #1c

The following table contains the test product formulation.

Ingredients	Pentazocine and Naloxone HCl Tablets, USP, equivalent to 50 mg/0.5 mg (amount per mg)
Pentazocine Hydrochloride, USP	56.4
Naloxone Hydrochloride, USP, Dihydrate	0.56
Microcrystalline Cellulose NF	[redacted]
D&C Green [redacted] Al-Lake blend Which is composed of:	[redacted]
Sodium Lauryl Sulfate NF	
Dibasic Calcium Phosphate NF	
Colloidal Silicon Dioxide NF	
Pregelatinized Starch NF	
Magnesium Stearate NF	
Total Weight (mg)	220.0

(b)4 - nfiden usines

The firm's response to comment #1c is acceptable.

Comment #1d

A comparative dissolution data on naloxone, comparing the test product and the reference listed product. The information should reflect a detailed description of the dissolution methodology (including type of equipment used) should be provided. In addition, the dates on which dissolution analysis were performed should be provided. It should be noticed that the Division of Bioequivalence considers the current USP methodology to be the regulatory method which must be used for dissolution comparison.

Response to Comment #1d

The firm's in vitro dissolution testing data for Naloxone are summarized in the following Table.

Table . In Vitro Dissolution Testing

Drug (Generic Name): Pentazocine HCl and Naloxone HCl
Dose Strength: 50 mg/0.5 mg
ANDA No.: 74-736
Firm: Royce
Submission Date: August 30, 1995
File Name: 74736a1.496

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT (b)4(Q) of the labeled amount of pentazocine is dissolved in 45 minutes.
Reference Drug: Sanofi Winthrop's Talwin® NX Tablets
Assay Methodology: (b)4 - Confidential

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Prod. Pentazocine HCl and Naloxone HCl Lot # LL-1535 ingredient: Naloxone HCl Strength(mg) 0.5			Reference Product Sanofi Winthrop's Talwin® NX Lot # B165LB ingredient: Naloxone HCl Strength(mg) 0.5		
	Mean %	Range	%C	Mean %	Range	%C
15	100.44	(b)4 - Confidential Business	1.9	88.97	(b)4 - Confidential Business	4.2
30	105.43		2.5	96.75		4.0
45	106.32		2.3	99.62		3.6
60	107.01		1.8	101.41		3.4

The firm's response to comment #1d is acceptable.

Comment #2

Clarify the major differences between the Linearity-clinical methodology that ranged from 5.0-800 ng/mL (Vol. #1.3, pages #1207-1209) and the Linearity-optimized sensitivity methodology that ranged from 2.0-50 ng/mL (Vol. #1.3, pages #1210-1211) and state which linearty method type was applied to calculate amount of the drug in plasma samples.

Response to Comment #2

The original pentazocine methodology was developed by (b)4 - and was referred to as clinical methodology. This method was modified prior to the firm's biostudy to improve the lower end of the linear range by revising the standard concentrations used; sample extraction and instrumentation were not modified in any way. The modified assay is referred to by (b)4 - as the optimized sensitivity methodology. The optimized sensitivity methodology was used for the biostudy. Some of the data in the validation report was obtained using the clinical methodology. Since sample extraction and instrumentation are the same, the results apply to both methods.

The firm's response to comment #2 is acceptable.

Comment #3

(b)4 - Confidential Business

Response to Comment #3

(b)4 - Confidential Business

The firm's response to comment #3 is acceptable.

Comment #4

Information on the batch/lot size and the date of manufacturing the test product should be included.

Response to Comment #4

Batch size (the actual yiel (b)4 - Confidential Business
The theoretical batch size:
The batch was manufactured on: 12/7/94 - 12/14/1994

The firm's response to comment #4 is acceptable.

Comment #5

State the rationale of including subjects who smoke.

Response to Comment #5

Subjects who smoke were included in the biostudy for ease of subject recruitment. The firm acknowledge Dr. Chan's letter (dated May 11, 1995) advising that the firm use non-smoking subjects due to a 1976 literature report that showed that smokers metabolize 40% more pentazocine than nonsmokers. However, the firm believes that this recommendation was for the purpose of reducing inter-subject variability and to make the test product easier to pass the bioequivalence requirments. The firm does not believe that metabolism of pentazocine affects absorption of products from the GI system. Since the firm's study results indicate that the test product is bioequivalent to the listed reference product in the biostudy which used mostly smoker subjects. Therefore, exclusion of smokers to reduce variability was not necessary.

The firm's response to comment #5 is acceptable.
Note: For future studies the firm is advised to restrict its subject inclusion criteria to non-smokers only.

RECOMMENDATIONS:

1. The two *in vivo* bioequivalence studies conducted by Royce Laboratories, Inc. under fasting and non-fasting conditions (ANDA #74-736; submission date 08/30/1995; review by Z. Wahba, Ph.D.) on its drug product, Royce's Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablets (Lot #LL-1535), comparing it to the reference drug product, Sanofi Winthrop's Talwin® NX Tablets (Lot #B165LB) have been found acceptable by the Division of Bioequivalence. Thus, Royce's Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablets is bioequivalent to the reference drug product, Sanofi Winthrop's Talwin® NX Tablets under fasting and non-fasting conditions .

2. The dissolution testing data conducted by Royce Laboratories, Inc. on its drug product, Royce's Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablets (Lot #LL-1535) have been found acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted using the following method: 900 mL, water at 37°C applying USP 23 Apparatus II (Paddle) at 50 rpm, [redacted] The test product should meet the following specifications:

   NLT [redacted] Q) of the labeled amount of the drug product in the capsule is dissolved in 45 minutes.

The firm should be informed of the recommendations.

[redacted] /S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED/RMHATRE

[redacted] /S/ 10/7/96

Concur: [redacted] /S/ Date: 10/8/96

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 74-736 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/091396/100496/file #74736a1.496

D W

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #74-736
SPONSOR: Royce Laboratories, Inc.
DRUG: Pentazocine HCl and Naloxone
DOSAGE FORM: Tablets
STRENGTH: 50 mg/0.5 mg
REFERENCE PRODUCT: Sanofi Winthrop's Talwin® NX Tablets.
TYPE OF STUDY: Single dose under fasting and non-fasting conditions
STUDY SITE:

/S/

STUDY SUMMARY: The two studies under fasting and non-fasting conditions are acceptable. The 90% confidence intervals for log-transformed pharmacokinetic parameters, AUC_{0-t}, AUC_{0-inf}, and C_{max} under fasting and non-fasting conditions for mexiletine were all within the acceptable range of 80 to 125%.

DISSOLUTION: The comparative dissolution testing data are acceptable.

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 10/9/96

BRANCH CHIEF: Ramakant Mhatre, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 10/9/96

DIRECTOR: Keith Chan, Ph.D.
for DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 10/17/96

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

2, V

FEB 12 1996

Pentazocine HCl and Naloxone HCl
50 mg/0.5 mg Tablets
ANDA #**74736**
Reviewer: ZZ Wahba
file #74736sd.895

Royce Laboratories, Inc.
Miami, Florida
Submission date:
August 30, 1995

REVIEW OF TWO IN VIVO BIOEQUIVALENCE STUDIES, AND IN VITRO DISSOLUTION TESTING DATA

I. OBJECTIVE:

To review:

1. Royce's two in vivo bioequivalence studies (single-dose fasting and single-dose post-prandial) comparing its test product Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablets to the reference listed product, Sanofi Winthrop's Talwin® NX Tablets.

2. Dissolution data for test and reference drug products.

II. BACKGROUND:

This drug is a combination of pentazocine HCl (equivalent to 50 mg base) and naloxone HCl (equivalent to 0.5 mg base). The drug is indicated for oral administration for the relief of moderate and severe pain.

Pentazocine is a synthetic opiate agonist analgesic and its chemical formula is 1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3 methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride.

Naloxone is inactive when administered orally in the amount (0.5 mg) present in this formulation, its presence does not interfere with the pharmacological action of pentazocine when the tablets are administered orally. However, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics. The inclusion of naloxone in this drug product is intended to curb a form of misuse of oral pentazocine. The presence of naloxone in this drug product will prevent the effect of pentazocine if the product is misused by injection. Studies in animals indicate that the presence of naloxone does not affect pentazocine analgesia when the combination is given orally. If the combination is given by injection the action of pentazocine is neutralized.

Pentazocine is well absorbed from the gastrointestinal tract. Peak concentrations occur 1 to 3 hours after oral administration. The plasma half-life is 2 to 3 hours. About 60% of pentazocine is bound to plasma proteins. Pentazocine is metabolized in the liver, mainly by oxidation of the terminal methyl groups of the dimethyl alkyl side chain to form alcoholic and carboxylic acid metabolites;

glucuronide conjugation also occurs. There is considerable inter-individual variation in the rate of metabolism and in the accumulative urinary excretion of the drug following oral administration (AHES Drug Information 93).

Pentazocine and Naloxone Hydrochlorides Tablets, 50 mg/0.5 mg is currently marketed under the trade name Talwin® NX Tablets (marketed by Sanofi Winthrop Pharmaceuticals).

III. Important Note:
On January 9, 1995 the firm submitted a bioequivalence study protocol (P#95-001) which proposed to measure only pentazocine in the plasma. Naloxone given orally at 0.5 mg dose level is not measurable in the blood, due to first pass metabolism in the liver.

On May 11, 1995 the Division of Bioequivalece issued a letter accepting the protocol and providing some comments. In the Division's response (dated May 11, 1995), the firm's proposal to measure only pentazocine was accepted.

In addition in the present submission the firm measured the level of naloxone in plasma and it was found to undetectable (zero) at all time points.

Therefore, in this bioequivalence study review only pentazocine will be evaluated.

IV. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER FASTING CONDITIONS

(clinical study project #9428004D)

A. Sponsor:
Royce Laboratories, Inc.
16600 NW 54 Avenue
Miami, FL 33014

Study site
Clinical Facilities (for housing the subjects)

(b)4 - Confidential

Analytical Facilities

(b)4 - Confidential Business

Statistical Facilities

(b)4 - Confidential Business

Study Dates:
Phase I: 05/23/1995
Phase II: 05/30/1995

B. Study design:

Randomized, single dose, two-way crossover study, under fasting conditions.

C. Subjects:

Thirty two (32) healthy male subjects were enrolled but only 31 subjects completed the clinical study. The subjects were in the range of 18 to 39 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection Criteria:

Only medically healthy subjects as determined by normal history, physical examination, laboratory profiles and ECG were enrolled in the study.

Subject Exclusion Criteria:

Subjects were excluded from the study based on the following criteria:

1. Allergy and/or sensitivity to pentazocine or naloxone or other related drugs.
2. Significant history of gastrointestinal or infectious diseases.
3. History of psychiatric disorders occurring within the last two years which required hospitalization and/or medication for more than 6 weeks.
4. Use of enzyme-inducing or enzyme-inhibiting drug(s) within 30 days prior to the entry into this study.
5. A history of chronic alcohol or drug addiction.
6. Blood donation or significant loss of blood within the past 30 days of the study.
7. Receiving any investigational drug within 30 days prior to period I dosing.
8. Positive a test results for drugs of abuse, hepatitis B or HIV antibodies.

Subject Restrictions:

1. No subject took any prescribed medications for at least 14 days prior to the beginning of the study and through out the study. No OTC medications were permitted for 72 hours before dosing in each study period.
2. No alcohol, xanthine and caffeine containing foods and beverages were allowed, beginning 48 hours prior to dosing until completion of the study.

3. Smoking was restricted from one hour before until 2 hours after each dose and for 30 minutes before each vital sign measurement.

D. Treatment Plan:

Test Product: 1 X Royce's Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablet, Lot #LL-1535, Batch size (not given), manufactured date (not given).

	assay	content uniformity
a. Pentazocine	97.32%	98.4% (%CV=0.7)
b. Naloxone	99.65%	100.4% (%CV=1.3)

Reference Product: 1 X Sanofi Winthrop's Talwin NX Tablet, Lot #B165LB, expiration date: 6/97.

	assay	content uniformity
a. Pentazocine	99.94%	100.46% (%CV=1.7)
b. Naloxone	99.58%	99.51% (%CV=1.7)

Washout period: 7 days between doses.

E. Drug, Food and Fluid Intake:

During the confinement periods of this study, the subjects were housed and fed at the clinical facility. Subjects fasted overnight (10 hours) before dosing and for 4 hours thereafter. Water ad libitum was allowed except for one hour before and 4 hours after dosing. The subjects received their medication with 240 mL of water. Standard, caffeine-free meals were provided at appropriate times thereafter (4, 10, 14 and 24 hours post-dose).

F. Blood sampling:

Blood samples (10 mL each) were collected at pre-dosing, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, 16, 20 and 24 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -20°C ± 5°C until analysis.

G. Adverse Events:

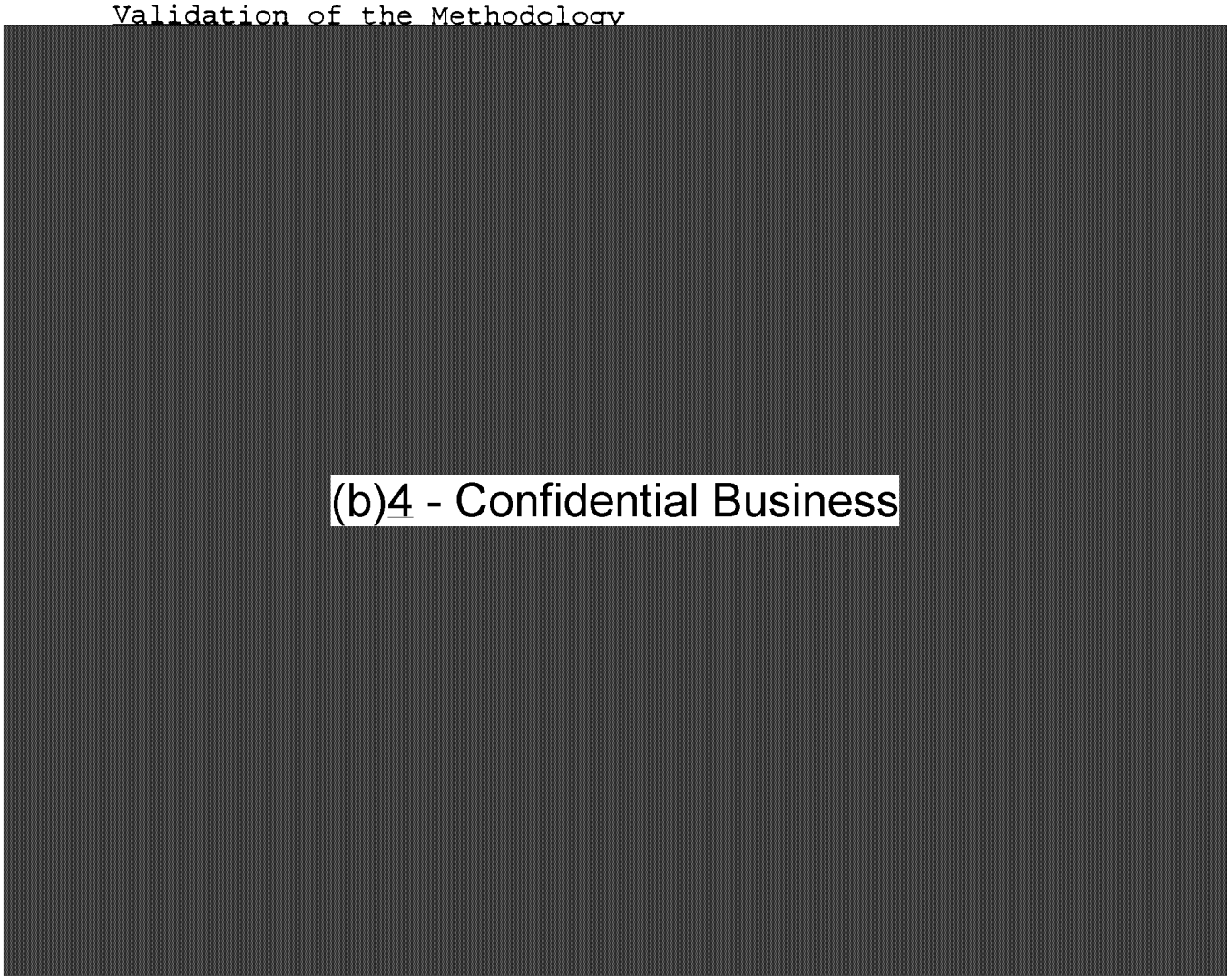
Summary of adverse events has been reported (ANDA #74736, vol. 1.1, p 124). Non of the adverse events experienced by the subjects during this study was judged as serious (see Attachment #1).

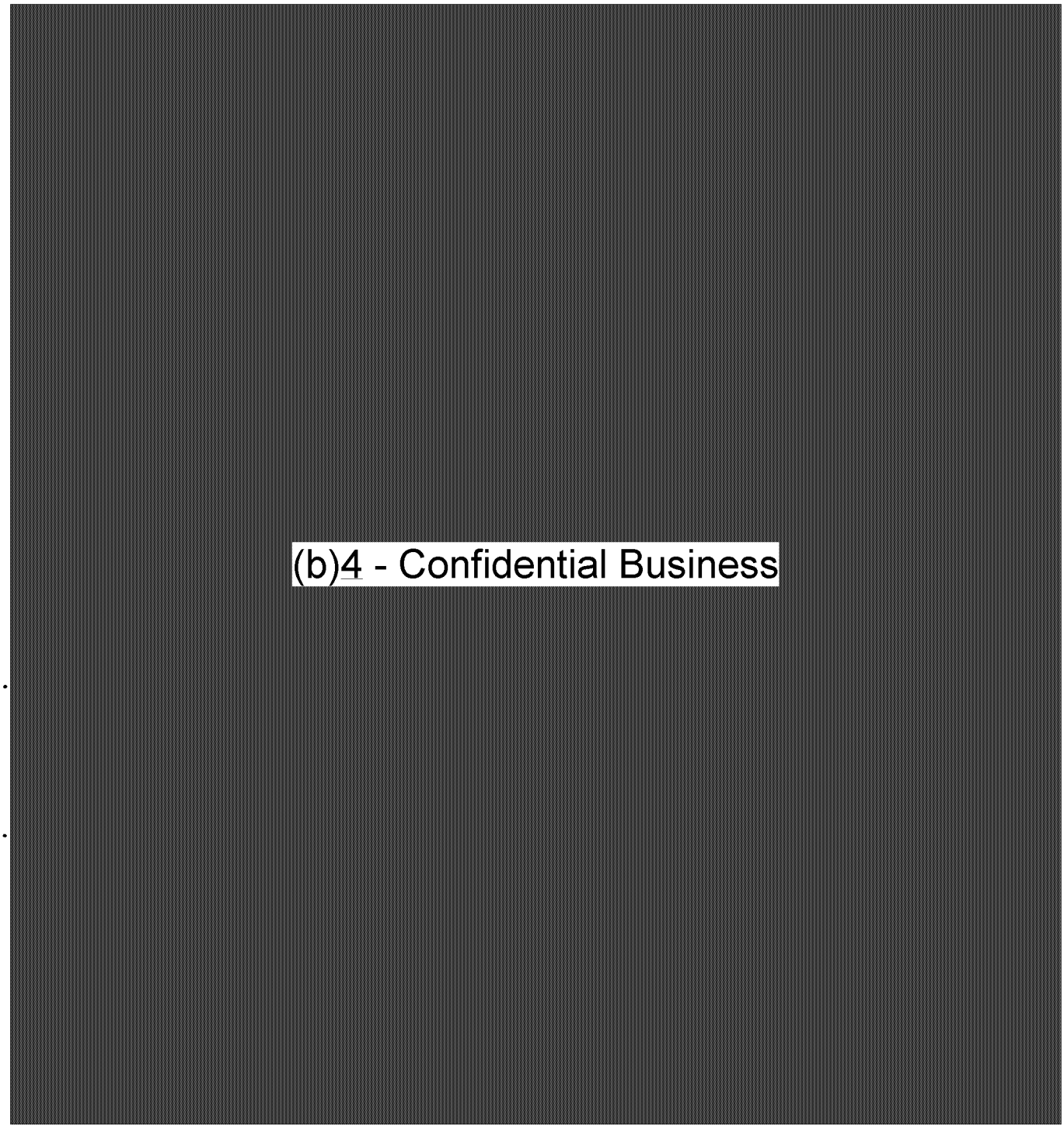
H. Assay Methodology:

Methods:

(b)4 - Confidential Business

Validation of the Methodology





4.

5.

I. **Statistical Analysis:**
The pharmacokinetic parameters of pentazocine were analyzed using the General Linear Models (GLM) procedure of the SAS statistical program. The statistical differences due to treatments, period, dosing sequence and subjects nested within

sequence were evaluated for plasma pentazocine concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$. The 90% confidence interval and the ratios of the test/reference means were also determined.

J. **In Vivo Data Analysis:**

Thirty two (32) healthy male subjects were enrolled but only 31 subjects completed the clinical study. Subject #22 withdrew from the study prior to dosing in Period II for personal reasons.

The firm used samples from 27 subjects for the statistical analysis due to a large analytical interference was reported in the pre-dose (Period I, test product) sample for subject #08 (at zero time = 10.6 ng/mL). Subjects #24, #28 and #32 had less than 5 measurable values from samples in one or both study periods preventing adequate characterization of their concentration-time profiles.

The next two statistical analysis data sections represent calculation of pentazocine plasma levels and pharmacokinetic parameters from 27 and 31 (including subjects #8, #24, #28, and #32) subjects, respectively.

a. Data Analysis (N=27):

The following statistical analysis were performed excluding the data from subjects #08, #24, #28 and #32 (n=27). The pharmacokinetic parameters of the plasma pentazocine concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$ for **27 subjects** are summarized in Tables #3-5.

Table 3
Mean Plasma Concentrations of Pentazocine
in 27 Subjects Under Fasting Conditions
Unit: ng/mL

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.00	0.00	0.11	0.58	0.00
0.5	1.90	2.87	2.04	3.04	0.93
0.75	6.74	6.53	8.95	8.66	0.75
1	15.39	12.88	13.26	12.06	1.16
1.5	18.72	13.77	**17.63**	15.20	**1.06**
2	**19.62**	14.57	16.41	11.14	**1.20**
2.5	16.31	11.16	15.93	11.72	1.02
3	16.94	13.54	17.28	13.28	0.98
4	14.70	11.90	12.91	10.59	1.14
6	10.97	10.18	9.58	7.05	1.14
8	7.39	7.34	6.94	7.43	1.06
10	5.01	6.17	5.10	5.77	0.98
12	4.23	5.54	3.17	3.85	1.33
16	2.09	3.86	2.37	3.79	0.88
20	1.04	3.10	1.12	3.09	0.93
24	0.52	1.52	0.44	1.59	1.19

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 4
Mean Pharmacokinetic Parameters
in 27 Subjects Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	127.59	122.54	139.05	145.58	0.92
AUCI	161.51	139.78	175.34	169.25	0.92
CMAX	21.39	14.62	21.66	15.79	0.99
KE	0.16	0.06	0.16	0.07	0.99
THALF	5.04	2.14	5.26	2.56	0.96
TMAX	1.88	0.68	1.97	0.85	0.95
*LAUCT	91.61	0.81	91.06	0.93	1.01
*LAUCI	124.73	0.70	122.18	0.85	1.02
*LCMAX	17.77	0.60	17.23	0.69	1.03

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
* The values represent the geometric means (antilog of the means of the logs).

Table 5
LSMEANS AND 90% CONFIDENCE INTERVALS (n=27)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCT	126.26	136.70	83.38	101.34
AUCI	154.45	169.11	81.17	101.49
CMAX	21.39	21.65	91.37	106.30
*LAUCT	90.79	89.63	92.46	110.98
*LAUCI	120.89	120.16	91.36	110.80
*LCMAX	17.79	17.24	93.88	113.41

Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the geometric means (antilog of the means of the logs).

1. The mean plasma pentazocine levels reached a maximum level of concentration around 1.5-2.0 hours (Table #3 and the attached Figures #1). Mean blood levels-time profiles were comparable between the test and reference products under the same conditions.

2. The arithmetic test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 0.92, 0.92 and 0.99, respectively. The geometric test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 1.01, 1.02 and 1.03, respectively (Table #4). The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of 80-125% (Table #5).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC and C_{max}.

3. The average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the reference product values (Table #4).

b. Analysis (N=31):
The following statistical analysis were performed including the data from subjects #08, #24, #28 and #32 (n=31).The pharmacokinetic parameters of the plasma pentazocine concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$ for **31 subjects** are summarized in Tables #6-10.

Table 6
Mean Plasma Concentrations of Pentazocine in 31 Subjects Under Fasting Conditions
Unit: ng/mL

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.34	1.90	0.00	0.00	.
0.25	0.33	1.83	0.10	0.54	3.40
0.5	2.05	3.30	1.77	2.91	1.15
0.75	6.59	6.47	8.21	8.54	0.80
1	14.29	12.85	13.14	13.17	1.09
1.5	18.06	14.82	**17.59**	17.17	**1.03**
2	**18.94**	16.09	16.33	13.69	**1.16**
2.5	16.71	15.14	16.16	14.31	1.03
3	16.74	15.24	17.07	15.16	0.98
4	15.34	15.97	12.90	12.77	1.19
6	11.51	13.56	9.50	8.67	1.21
8	7.94	10.16	7.12	8.39	1.11
10	5.47	7.98	5.36	6.70	1.02
12	4.81	7.72	3.52	5.24	1.37
16	2.64	5.58	2.75	4.98	0.96
20	1.34	3.68	1.50	3.99	0.89
24	1.05	3.54	0.84	2.89	1.25

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 7
Mean Pharmacokinetic Parameters in 31 Subjects Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	138.89	176.70	143.13	171.29	0.97
AUCI	199.68	234.86	201.61	233.40	0.99
CMAX	21.33	17.57	21.31	17.45	1.00
KE	0.15	0.06	0.17	0.11	0.90
THALF	5.26	2.35	5.53	3.38	0.95
TMAX	1.98	0.76	1.94	0.85	1.02
*LAUCT	76.15	1.19	73.36	1.31	1.04
*LAUCI	136.15	0.81	121.96	1.02	1.12
*LCMAX	15.79	0.81	15.58	0.83	1.01

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table 8
LSMEANS AND 90% CONFIDENCE INTERVALS (n=31)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCT	139.18	142.95	87.35	107.38
AUCI	186.58	194.05	86.54	105.76
CMAX	21.36	21.33	93.08	107.20
*LAUCT	75.84	72.93	94.21	114.80
*LAUCI	122.69	121.74	92.23	110.11
*LCMAX	15.79	15.58	92.99	110.45

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the geometric means (antilog of the means of the logs).

Table 9
Test/Reference Products Ratios
for Pharmacokinetic Parameters for Individual Subjects (n=31)

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	1	(b)4 - Confidential Business					
2	2	1						
3	3	1						
4	4	2						
5	5	2						
6	6	1						
7	7	1						
8	8	1						
9	9	1						
10	10	2						
11	11	2						
12	12	1						
13	13	2						
14	14	2						
15	15	2						
16	16	2						
17	17	2						
18	18	1						
19	19	2						
20	20	2						
21	21	1						
22	23	2						
23	24	1						
24	25	2						
25	26	1						
26	27	2						
27	28	2						
28	29	1						
29	30	1						
30	31	2						
31	32	1						

1=Test product 2=Reference product

Table 10
Summary of Mean and SD of Individual T/R Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	31	1.09	0.39	(b)4 - Confidential Business	
RAUCI12	22	1.02	0.28		
RCMAX12	31	1.05	0.30		
RTMAX12	31	1.26	0.77		
RKE12	22	1.14	0.39		
RTHALF12	22	0.98	0.34		

1. The mean plasma pentazocine levels reached a maximum level of concentration around 1.5-2.0 hours (Table #6). Mean blood levels-time profiles were comparable between the test and reference products under the same conditions.

2. The arithmetic test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 0.97, 0.99 and 1.00, respectively. The geometric test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 1.04, 1.12 and 1.01, respectively (Table #7). The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of 80-125% (Table #8).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC and C_{max}.

3. The average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the reference product values (Table #7).

General Comments on In Vivo Data Analysis (N=31) and (N=27)
The statistical analysis for AUC_{0-t}, AUC_{0-inf} and C_{max} for the 31 subjects and 27 subjects (excluding subjects #8, 24, 28 and 32) were within the acceptable range of 80-125% that has been set by the Division of Bioequivalence.

V. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER NON-FASTING CONDITIONS

(clinical study project #9528015D)

A. Sponsor:

(b)4 - Confidential Business

Study site
Clinical and Analytical Facilities
The same as protocol #9428004D

Principle Investigato[redacted] (b)4 - Confidential Business

Study Dates:
Phase I: 6/10/1995
Phase II: 6/17/1995
Phase III: 6/24/1995

B. **Study design:**
Randomized, three-way single dose crossover study, under non-fasting conditions.

C. **Subjects:**
Eighteen (18) healthy male subjects were enrolled but 17 subjects completed the clinical study. The subjects were in the range of 19 to 40 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Exclusion Criteria and Subject Restrictions:
The same as under fasting condition.

D. **Treatment Plan:**
Treatment A: 1 X Royce's Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablet, Lot #LL-1535, Batch size (not given), manufactured date (not given), under non-fasting conditions.

	assay	content uniformity
a. Pentazocine	97.32%	98.4% (%CV=0.7)
b. Naloxone	99.65%	100.4% (%CV=1.3)

Treatment B: 1 X Royce's Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablet, Lot #LL-1535, Batch size (not given), manufactured date (not given), under fasting conditions.

	assay	content uniformity
a. Pentazocine	97.32%	98.4% (%CV=0.7)
b. Naloxone	99.65%	100.4% (%CV=1.3)

Treatment C: 1 X Sanofi Winthrop's Talwin NX Tablet, Lot #B165LB, expiration date: 6/97, under non-fasting condition.

	assay	content uniformity
a. Pentazocine	99.94%	100.46% (%CV=1.7)
b. Naloxone	99.58%	99.51% (%C=1.7)

Washout period: 7-day washout between doses.

E. **Drug, Food and Fluid Intake:**
Subjects who received treatments A and C, fasted overnight for 10 hours before they were fed a standard high fat breakfast, which was consumed in its entirety 15 minutes before drug administration.

Each dose was followed by 240 mL of room temperature tap water according to randomized dosing schedule. Subjects who received treatment B, fasted overnight for 10 hours before dosing and for 4 hours after each drug administration. Standard meals were provided at appropriate times thereafter at 4 hrs (lunch), 10 hrs (dinner), 14 hrs (snack) and 24 hrs (day-2, breakfast) after drug administration.

F. Blood sampling:

Blood samples (10 mL each) were collected at pr-dosing, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12, 16, 20 and 24 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -20°C ± 5°C until analysis.

G. Adverse Events:

Summary of adverse events have been reported (ANDA #74736, vol. C1.3, p 1258). None of the adverse events experienced by the subjects during this study was judged as serious (see Attachment #2).

H. Protocol Deviations:

1. Subject #10 did not eat the soup at lunch in Period II, Subject #15 did not eat the cheese at lunch in Periods II and III.

2. Subject #14 reported taking 400 mg of ibuprofen on 6/15/95, 36 hours prior II dosing. He was permitted to continue in the study by investigator.

I. Assay Methodology:

Methods and Validation:

The same as under fasting condition.

J. Data Analysis:

Eighteen subjects was entered the study and 17 subjects completed the study. Subject #5 was withdrawn from the study prior to dosing in Period II because of a positive urine drug screen. He received one dose of the reference formulation. The pharmacokinetic parameters of pentazocine were analyzed using an analysis of variance. The statistical differences due to treatments, period, dosing sequence and subjects nested within sequence were evaluated for plasma pentazocine concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$. The ratios of the test/reference means were also determined.

The pharmacokinetic parameters of the plasma pentazocine concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$ are summarized in Tables #11&12.

Table 11
Mean Plasma Concentrations of Pentazocine
in 17 Subjects Under Non-Fasting Conditions
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.25	0.00	0.00	0.00	0.00	0.00	0.00
0.5	1.39	2.14	3.42	6.04	3.85	6.17
0.75	7.87	6.40	8.84	8.96	13.05	16.11
1	15.36	12.43	15.29	13.17	18.13	15.21
1.5	22.99	14.02	18.58	14.04	22.29	14.31
2	24.29	12.14	**19.85**	15.55	**25.84**	16.71
3	**24.34**	13.47	18.34	13.33	23.65	15.12
4	22.67	14.97	14.52	12.91	19.08	**11.80**
6	15.19	12.89	12.16	12.47	13.96	11.11
8	10.98	10.35	8.36	8.66	11.53	12.27
10	7.81	9.11	6.29	6.55	9.03	10.35
12	6.06	8.16	4.63	6.46	6.18	7.88
16	3.82	6.78	3.02	4.84	3.79	5.71
20	2.54	5.15	2.11	4.50	2.12	4.90
24	1.45	3.71	1.11	3.15	0.84	2.68

MEAN1=Test-Fed MEAN2=Test-Fast MEAN3=Reference-Fed
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

(CONTINUED)

TIME HR	RMEAN12	RMEAN13	RMEAN23
0	.	.	.
0.25	.	.	.
0.5	0.41	0.36	0.89
0.75	0.89	0.60	0.68
1	1.00	0.85	0.84
1.5	1.24	1.03	0.83
2	1.22	**0.94**	0.77
3	1.33	**1.03**	0.78
4	1.56	1.19	0.76
6	1.25	1.09	0.87
8	1.31	0.95	0.73
10	1.24	0.86	0.70
12	1.31	0.98	0.75
16	1.27	1.01	0.80
20	1.20	1.20	1.00
24	1.31	1.74	1.32

Table 12
Mean Pharmacokinetic Parameters of Pentazocine in 17 Subjects Under Non-Fasting Conditions
Unit: ng/mL

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
AUCT	206.31	180.13	158.40	168.55	201.47	181.90
AUCI	251.42	233.38	200.53	222.95	219.33	189.82
CMAX	30.10	16.73	22.48	16.49	31.04	18.30
KE	0.16	0.07	0.13	0.06	0.14	0.05
*LAUCT	154.55	0.76	107.76	0.85	153.05	0.73
*LAUCI	186.15	0.76	137.15	0.81	175.67	0.64
*LCMAX	25.95	0.57	17.83	0.69	25.98	0.64
THALF	5.39	2.86	6.64	3.40	5.70	2.48
TMAX	2.03	0.80	2.00	0.77	2.09	0.75

MEAN1=Test-Fed MEAN2=Test-Fast MEAN3=Reference-Fed
RMEAN13=T/R ratios (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
AUCT	1.30	1.02	0.79
AUCI	1.25	1.15	0.91
CMAX	1.34	0.97	0.72
KE	1.23	1.13	0.92
THALF	0.81	0.95	1.17
TMAX	1.01	0.97	0.96
*LAUCT	1.43	**1.01**	0.70
*LAUCI	1.36	**1.06**	0.78
*LCMAX	1.45	**1.00**	0.69

1. Under non-fasting conditions, the mean plasma levels for pentazocine reached the maximum around 2.0-3.0 hours (Table #11 and Figure #2). Mean blood levels-time profiles were comparable between the test and reference products under the same conditions. However, the results show a significant food effect on the pharmacokinetics parameters of pentazocine when the drug is given with food.

2. The test/reference mean ratios under non-fasting conditions for the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the acceptable range of 0.8 to 1.2 that has been set by the Division of Bioequivalence.

3. Under non-fasting conditions the average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the reference product values.

VI. IN VITRO DISSOLUTION TESTING

The firm has submitted in vitro dissolution testing data for its drug product, Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablets.

Method:	USP 23 apparatus II (Paddles) at 50 rpm
Medium:	Water
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Reporting Intervals:	15, 30, 45 and 60 minutes
No. Units Tested:	12 Tablets
Specification:	NLT (b)4(Q) of the labeled amount of pentazocine is dissolved in 45 minutes
Reference product:	Sanofi Winthrop's Talwin NX Tablets
Test Lot#:	LL-1535
Reference Lot#:	B165LB

Table 13. In Vitro Dissolution Testing

Drug (Generic Name): Pentazocine HCl and Naloxone HCl
Dose Strength: 50 mg/0.5 mg
ANDA No.: 74-736
Firm: Royce
Submission Date: August 30, 1995
File Name: 74736sd.895

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT (b)4 (Q) of the labeled amount of pentazocine is dissolved in 4[redacted] minutes.
Reference Drug: Sanofi Winthrop's Talwin® NX Tablets
Assay Methodology: (b)4 - Confidential

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Prod. Pentazocine HCl and Naloxone HCl Lot # LL-1535 Dissolution of the active ingredient: Pentazocine HCl Strength(mg) 50			Reference Product Sanofi Winthrop's Talwin® NX Lot # B165LB Dissolution of the active ingredient: Pentazocine HCl Strength(mg) 50		
	Mean %	Range	%C	Mean %	Range	%C
15	81.5	(b)4 - Confidential Business	7.6	74.1	(b)4 - Confidential Business	4.9
30	91.9		6.0	85.3		3.4
45	96.8		4.0	91.1		2.4
60	98.8		3.1	94.0		2.4

VII. COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Royce's Pentazocine Hcl/Naloxone Hcl (50 mg/0.5 mg) Tablets and the reference product, Sanofi Winthrop's Talwin® NX Tablets are bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-} and C_{max} were all within the acceptable range of 80-125%. The statistical analysis for AUC_{0-t}, AUC_{0-inf} and C_{max} for the 31 subjects and 27 subjects (excluding subjects #8, 24, 28 and 32) were within the acceptable range of 80-125% that has been set by the Division of Bioequivalence.

2. Under non-fasting conditions: The in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Royce's Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg)

Tablets and the reference product, Sanofi Winthrop's Talwin® NX Tablets are bioequivalent. The ratios of the test mean to the reference mean for the AUC_{0-t}, $AUC_{0-\infty}$, C_{max} were within the acceptable range of 0.8 to 1.2 that has been set by the Division of Bioequivalence. In general, the results show a significant food effect on the pharmacokinetics parameters of pentazocine when the drug is given with food.

VIII. DEFICIENCIES:

1. The following items on pentazocine are missing from the submission:

   a. Provide the raw data of the long-term freezing (-20°C) stability (the stability data should cover the entire length of the study). In addition, the raw data of the effect of room temperature during handling of the samples, and the effect of freeze and thaw cycles should be included.

   b. The raw data of pentazocine-recovery analytical methodology.

   c. Statement of the chemical composition (formulation) of the tested drug. The statement should include all active and inactive ingredients and the exact quantity of each component.

   d. A comparative dissolution data on naloxone, comparing the test product and the reference listed product. The information should reflect a detailed description of the dissolution methodology (including type of equipments that were used) should be provided. In addition, the dates which dissolution analysis were performed should be provided. It should be noticed that the Division of Bioequivalence considers the current USP methodology to be the regulatory method which must be used for dissolution comparison.

2. (b)4 - Confidential Business

3. (b)4 - Confidential Business

provide an explanation.

4. Information on the batch/lot size and the date of manufacturing the test product should be included.

5. State the rationale of including subjects who smoke.

VI. RECOMMENDATIONS:

The in vivo bioequivalence study conducted by Royce Laboratories, Inc. under fasting and non-fasting conditions on its drug product, Royce's Pentazocine HCl/Naloxone HCl (50 mg/0.5 mg) Tablets comparing it to the reference drug product, Sanofi Winthrop's Talwin® NX Tablets has been found incomplete by the Division of Bioequivalence for the deficiencies cited above (#1-5).

The firm should be informed of the deficiencies and recommendations.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/

Concur: /S/ Date:

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-736 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/013196/020896/file #74736sd.895

Figure #1
(under fasting conditions) STUDY NO. 9428004D

LEAST-SQUARES MEAN PENTAZOCINE PLASMA CONCENTRATIONS (N=27)

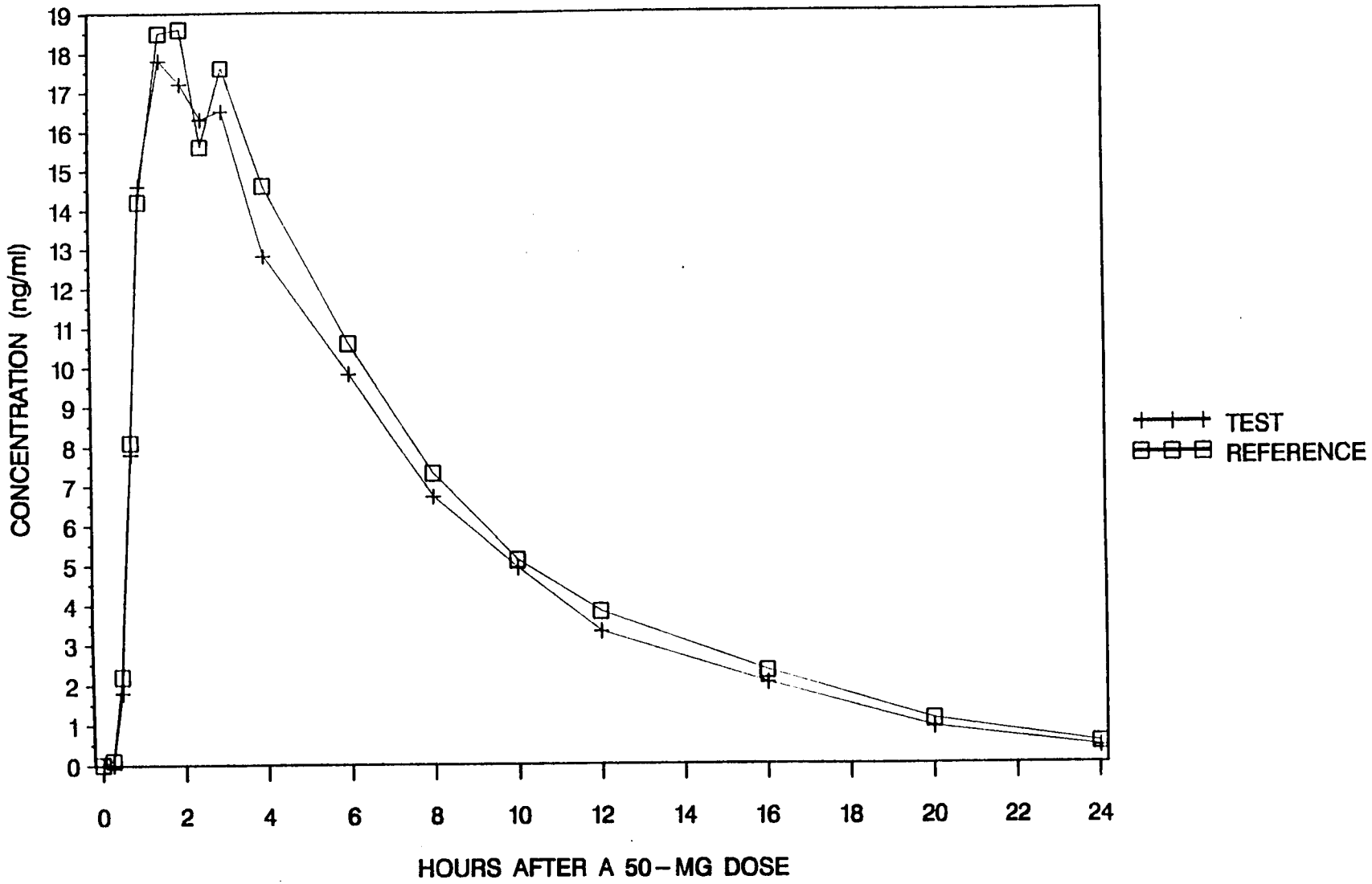
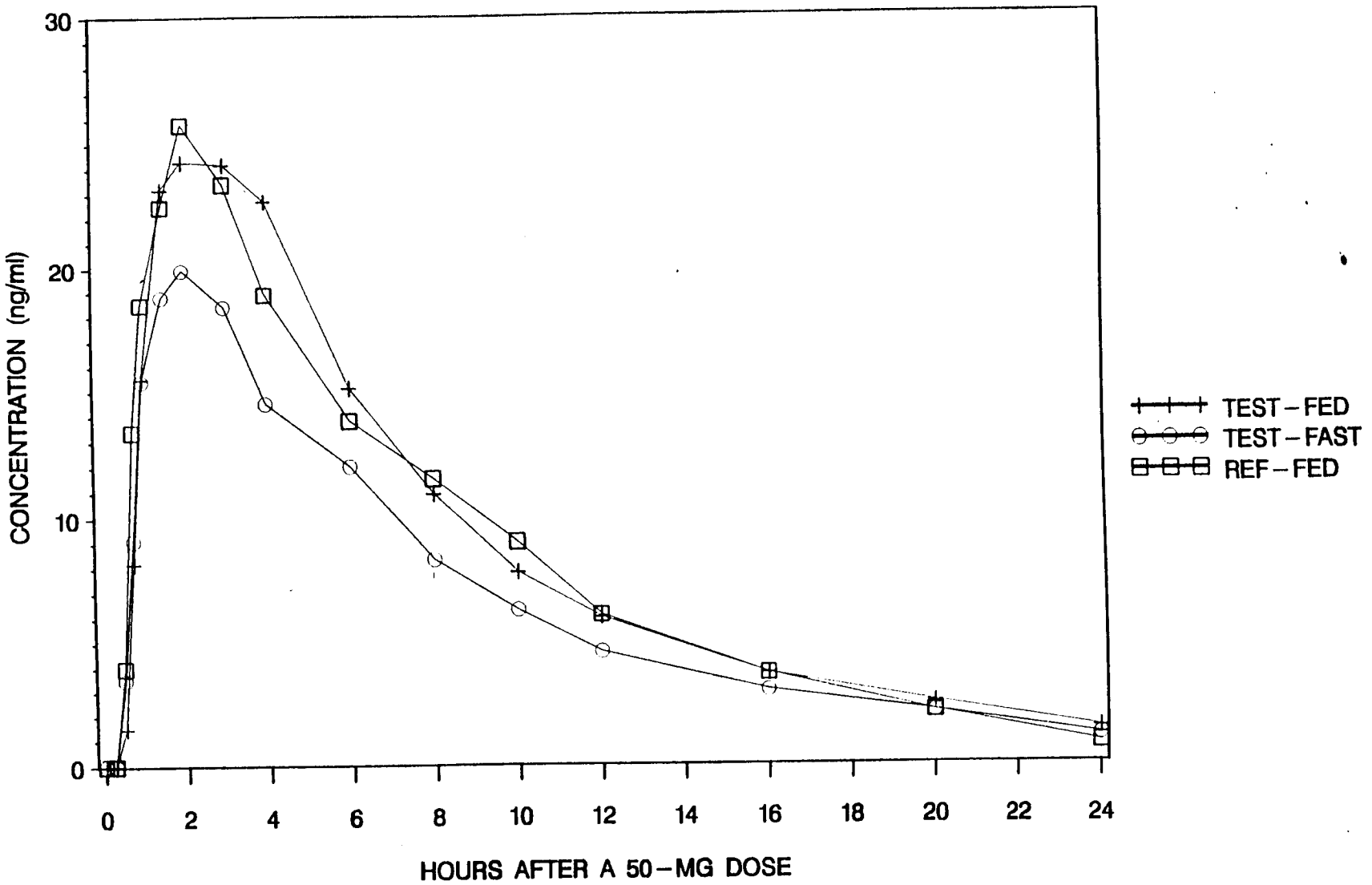


Figure #2
(under non-fasting conditions)

STUDY NO. 9528015D

LEAST-SQUARES MEAN PENTAZOCINE PLASMA CONCENTRATIONS (N=17)



Attachment #1

PENTAZOCINE / NALOXONE STUDY NO. 9428004D

Table C3: Summary of Adverse Events

Subject	Trt*	Adverse Event	ONSET		END		Sev[1]	Rel[2]	Treatment Given, or Comment
			Date	Time	Date	Time			
003	B	Lightheadedness	5/30/95	0900	5/30/95	1100	1	2	None
004	A	Dizziness	5/30/95	0900	5/30/95	0945	1	3	None
007	B	Drowsiness	5/30/95	0900	5/30/95	1100	1	4	None
008	A	Sense of well being	5/23/95	0900	5/23/95	1300	1	1	None
008	B	Drowsiness	5/30/95	0900	5/30/95	1200	1	4	None
008	B	Dry mouth	5/30/95	0900	5/30/95	1200	1	1	None
011	A	Drowsiness	5/30/95	0900	5/30/95	1100	1	4	None
013	B	Lightheadedness	5/23/95	0900	5/23/95	1300	1	3	None
018	A	Tiredness	5/23/95	0915	5/23/95	1115	1	3	None
023	B	Drowsiness	5/23/95	0930	5/23/95	1230	1	4	None
023	A	Lightheadedness	5/30/95	0900	5/30/95	1130	1	3	None
026	Pre-dose	Headache	5/20/95	0845	5/25/95	1300	1	1	None
026	B	Lightheadedness	5/30/95	0900	5/30/95	1115	1	3	None
028	B	Drowsiness	5/23/95	0915	5/23/95	1130	1	4	None
028	A	Drowsiness	5/30/95	0900	5/30/95	1100	1	4	None
029	A	Drowsiness	5/23/95	0850	5/23/95	1300	1	4	None
029	B	Lightheadedness	5/30/95	0900	5/30/95	1300	1	3	None
030	A	Drowsiness	5/23/95	0910	5/23/95	1100	1	4	None
030	B	Drowsiness	5/30/95	0900	5/30/95	1300	1	4	None

* Treatment: A-Test; B-Reference.
[1] Severity of Adverse Event: 1-Mild; 2-Moderate; 3-Severe.
[2] Relationship of Event to Drug: 1-None; 2-Remote; 3-Possible; 4-Probable; 5-Highly probable.

Attachment #2

PENTAZOCINE / NALOXONE STUDY NO. 9528015D

Table C3: Summary of Adverse Events (Page 1 of 3)

Subject	Trt*	Adverse Event	ONSET		END		Sev[1]	Rel[2]	Action or Comment
			Date	Time	Date	Time			
01	C	Tiredness	6/24/95	0930	6/24/95	1800	1	4	
02	B	Lightheadedness	6/17/95	0945	6/17/95	1430	1	3	
02	B	Tiredness	6/17/95	0945	6/17/95	1430	1	4	
02	A	Lightheadedness	6/24/95	0925	6/24/95	1100	1	4	
05	C	Somnolence	6/10/95	0900	6/10/95	0930	1	4	"Relaxed feeling"
06	C	Somnolence	6/10/95	0930	6/10/95	1000	1	4	"Relaxed feeling"
07	C	Lightheadedness	6/10/95	0900	6/10/95	0930	1	3	Cold compress applied to neck.
07	A	False sense of well-being	6/17/95	0900	6/17/95	1100	1	4	
09	C	Mouth injury	6/12/95	1015	6/23/95	1615	2	1	Teeth loosened and lip split in job-site accident. No medication taken.
09	B	Headache	6/17/95	0930	6/18/95	0400	1	3	Ice pack applied.
09	B	Nausea	6/24/95	1108	6/24/95	1430	1	4	
09	B	Headache	6/24/95	0900	6/24/95	2100	1	3	Attributes to eye strain.
10	A	Drowsiness	6/17/95	0830	6/17/95	1047	1	4	
10	C	Tiredness	6/24/95	0830	6/24/95	1130	1	4	
11	B	Somnolence	6/10/95	1000	6/10/95	1015	1	4	Feels relaxed.
11	C	False sense of well-being	6/17/95	1000	6/17/95	1230	1	4	
12	B	Lightheadedness	6/10/95	0930	6/10/95	1000	1	4	Advised to rise slowly.
12	C	Tiredness	6/17/95	0930	6/17/95	1800	1	5	

* Treatment: A-Test-Fed; B-Test-Fast; C--Reference.
[1] Severity of Adverse Event: 1-Mild; 2-Moderate; 3-Severe.
[2] Relationship of Event to Drug: 1-None; 2-Remote; 3-Possible; 4-Probable; 5-Highly probable.

(42 CFR)

PENTAZOCINE / NALOXONE STUDY NO. 9528015D

Table C3: Summary of Adverse Events (Page 2 of 3)

Subject	Trt*	Adverse Event	ONSET		END		Sev[1]	Rel[2]	Action or Comment
			Date	Time	Date	Time			
12	A	Tiredness	6/24/95	0900	6/24/95	1100	1	4	
12	A	Lightheadedness	6/24/95	0900	6/24/95	1100	1	4	
13	A	Lightheadedness	6/10/95	1000	6/10/95	1030	1	4	Advised to rise slowly.
13	B	Tiredness	6/17/95	0830	6/17/95	1800	1	5	
13	C	False sense of well-being	6/24/95	0830	6/24/95	1000	1	4	
14	B	Lightheadedness	6/17/95	0900	6/17/95	1100	1	3	
14	B	Tiredness	6/17/95	1030	6/17/95	1810	1	5	
15	B	Sweating	6/10/95	1000	6/10/95	1015	1	2	Cold sweat, forehead & arms.
15	B	Upset stomach	6/10/95	1000	6/10/95	1030	1	1	Felt nauseous.
15	B	Lightheadedness	6/10/95	1000	6/10/95	1400	1	4	Advised to rise slowly.
15	B	Headache	6/10/95	1345	6/10/95	2230	1	3	
15	B	Pain in right eye	6/11/95	0900	6/12/95	1400	1	1	
15	C	Pain in right eye	6/17/95	0840	6/18/95	0015	1	1	
15	C	Nausea	6/17/95	1045	6/17/95	1200	1	4	Cool compress applied, laid down.
15	C	Lightheadedness	6/17/95	0850	6/17/95	1900	1	3	
15	C	Headache	6/17/95	1045	6/17/95	1900	1	3	
15	A	Lightheadedness	6/24/95	1010	6/24/95	2200	1	4	
15	A	Tiredness	6/24/95	0837	6/24/95	1600	1	4	
15	A	Dizziness	6/24/95	1200	6/24/95	2030	1	4	
15	A	Nausea	6/24/95	1200	6/24/95	2030	1	4	
16	A	Lightheadedness	6/17/95	1000	6/17/95	1415	1	3	Advised to rise slowly.
16	A	Tiredness	6/17/95	1000	6/17/95	1415	1	5	

* Treatment: A-Test-Fed; B-Test-Fast; C--Reference.
[1] Severity of Adverse Event: 1-Mild; 2-Moderate; 3-Severe.
[2] Relationship of Event to Drug: 1-None; 2-Remote; 3-Possible; 4-Probable; 5-Highly probable.

(27)

PENTAZOCINE / NALOXONE STUDY NO. 9528015D

Table C3: Summary of Adverse Events (Page 3 of 3)

Subject	Trt*	Adverse Event	ONSET		END		Sev[1]	Rel[2]	Action or Comment
			Date	Time	Date	Time			
17	A	Dizziness	6/10/95	0900	6/10/95	1000	1	3	
17	A	Lightheadedness	6/10/95	0900	6/10/95	1000	1	4	Advised to rise slowly.
17	C	Lightheadedness	6/17/95	0900	6/17/95	0945	1	3	
18	C	False sense of well-being	6/17/95	0920	6/17/95	1030	1	4	

* Treatment: A-Test-Fed; B-Test-Fast; C--Reference.
[1] Severity of Adverse Event: 1-Mild; 2-Moderate; 3-Severe.
[2] Relationship of Event to Drug: 1-None; 2-Remote; 3-Possible; 4-Probable; 5-Highly probable.